REMARKS

Claims 37 and 39 have been amended to include the limitations of "green or blue fluorescent protein" and "green or blue fluorescent protein in an internal organ", which are clearly supported by the specification. *See*, for example, page 23, lines 12-15 and Examples 1 and 2 on pages 32-36 and throughout the specification. Thus, no new matter is added.

Applicants respectfully request that the Examiner exercise her discretion and enter this amendment though made after final. The amendment clearly places the claims in a position for allowance as the limitation overcomes the outstanding rejection. Entry of the amendment is therefore respectfully requested.

Applicants very much appreciate the withdrawal of a rejection that had been made previously.

Claims 37 and 39 are patentable under 35 U.S.C. § 103.

Claims 37 was rejected as allegedly obvious over U.S. Patent No. 5,650,135 to Contag et al. ("Contag") in view of Okabe et al., *FEBS Letters* 407:313-319, 1997 ("Okabe").

While the strict teaching - suggestion - motivation (TSM) test was rejected by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, there nonetheless must be an "articulated reasoning with some rational underpinning to support the legal conclusion" of obviousness. 82 U.S.P.Q.2d 1385, at 1396 (S. Ct. 2007). Determining if there is an articulated reason requires analysis of a number of factors, which include whether there is evidence of teaching away and whether there is a reasonable expectation of success.

Applicants have achieved a result not taught or suggested in the cited prior art: the detection of GFP expression from internal organs of a non-human laboratory mammal. *See* Examples 1 and 2

on pages 32-35 of the specification as filed. As described on pages 32-34, GFP expression was engineered in various internal organs, such as liver, brain, pancreas, prostate, and bone marrow. In the carryover paragraph on pages 34-35, Applicants reveal a quantitative method that allows for detecting a blue or green fluorescent protein in internal organs while corrects for the intrinsic red fluorescence of the mouse's skin.

Contag teaches away from the presently claimed subject matter. Contag suggests that bioluminescent markers, such as luciferase, might be successfully detected in a mammal while also suggesting that detection of green fluorescent protein in an internal organ of a mammal is not likely to be successful. Claim 37 is directed to an animal that expresses a blue or green fluorescent protein in an internal organ. Blue or green fluorescent proteins emit at a shorter wavelength than luciferase. Contag teaches that "LGMs which emit light in the range of yellow to red (550 – 1100 nm) are typically prefereable to LGMs which emit at shorter wavelengths." *See* column 8, lines 42-44.

Contag also states that:

> [E]xcellent results can be achieved in practicing the present invention with LGMs that emit in the range of 486 nm, despite the fact that this is not an optimal emission wavelength. These results are possible, in part, due to the relatively high concentration of LGMs (luciferase molecules) present in the LECs (transformed *Salmonella* cells) used in these experiments, and to the use of a sensitive detector. It will be understood that through the use of LGMs with a more optimal emission wavelength, similar detection results can be obtained with LGEs having lower concentrations of the LGMs. *See* column 8, lines 47-57.

It is clear from the teachings of Contag that successful detection of blue or green fluorescent protein is not expected according to the claimed method, unless GFP is concentrated to a degree as found within a transformed *Salmonella* cell. Based on these teachings, one of skill in the art would be guided to choose luciferase instead of GFP. Contag therefore teaches away from use of these proteins.

This viewpoint was reiterated and emphasized by Chistopher Contag in Contag et al., "Use of Reporter Genes for Optical Measurements of Neoplastic Disease *In Vivo*" *Neoplasia,* 2:41-52, 2000 ("Contag article"), attached as Exhibit A. Page 44, second full paragraph, states:

> Bioluminescent reporters may offer greater versatility than fluorescent or other types of markers in mammalian tissues due to the nearly complete absence of spontaneous emission of light from mammalian cells. The use of outside light sources for fluorescence markers can result in tissue autofluorescence, creating background that is greater than the signal.

One of skill in the art would understand that luciferase is an exemplary bioluminescent reporter while blue or green fluorescent proteins are an exemplary fluorescence marker. The Contag article only describes GFP in the context of intravital microscopy in which tissue over the tumor must be excised to permit visualization of the GFP-labelled cells. *See* the first full paragraph on page 48. For tumor imaging and to detect labeled cells "several millimeters or centimeters within mammalian tissue", Contag recommends use of orange or red fluorescence labels since these longer wavelengths transmit through tissues more efficiently than green light. *See* the second full paragraph on page 48.

Contag's disclosure teaches away from the successful detection of blue and green fluorescent proteins according to the claimed subject matter. Applicants describe successful detection of green or blue fluorescent proteins in internal organs despite the less efficient transmission of green light and the high red autofluorescence of mouse skin described by Contag. The successful detection was conducted, for example, by the use of the quantitative method taught on pages 34 and 35 of the specification. For these reasons, the disclosure of Contag, as further discussed in the Contag article, teaches away from the claimed methods.

The combination of Okabe with Contag actually teaches away from the invention. Okabe teaches production of green fluorescent protein under control of a chicken β actin promoter and a cytomegalovirus enhancer resulting in fluorescence in all of the tissues, with the exception of erythrocytes and hair. Combining Okabe with Contag, then, would not permit the localization of gene expression in internal organs as required by the claims, because the GFP is ubiquitously expressed. For instance, if GFP is expressed in the skin and other outer tissues as well as in internal organs, it would be difficult to follow Okabe's teachings to detect changes of expression of GFP in an internal organ because the GFP expression in skin and outer tissues would completely obscure the GFP in an internal organ. Therefore, this combination does not result in or suggest the claimed invention.

Contag and Okabe also do not provide a reasonable expectation of success with regard to claim 37. As discussed above, Contag only teaches that detection of GFP in an internal organ would ordinarily not be successful because it is not of the optimal wavelength and the tissue autofluorescence from the external light source. Okabe does not suggest success because it would be apparent to one of ordinary skill in the art that the GFP expression in the skin and outer tissues

would serve as a strong background to the GFP expression in an internal organ such that the detection and comparison steps (b) and (c) of claim 37 could not be conducted successfully.

Claim 39 was rejected as allegedly obvious over U.S. Patent No. 6,380,458 to Lin et al. ("Lin") in view of Contag and Okabe.

The Examiner cited column 7, line 11 and column 11, lines 10-18 of Lin as allegedly teaching the creation of genetically modified zebrafish expressing green fluorescent protein. However, the teachings of Lin are not relevant to the claimed subject matter because a key difference between the zebrafish of Lin and the non-human mammalian laboratory animal of the claimed subject matter is that zebrafish are transparent.

Lin states that the transparency of zebrafish is an aspect that makes them the most preferred fish for use with the disclosed constructs. *See* column 8, lines 18-21. These statements in Lin suggest that it may be difficult to detect GFP in a non-transparent mammal, such as a mouse, and Lin does not provide further teaching that detection of GFP within a non-transparent mammal is likely to be successful. As described above, Contag teaches that autofluorescence of the skin of a mammal renders GFP detection difficult and it is clear from Okabe that GFP expression in the skin obscures detection of GFP in an internal organ. Because of these problems of detecting green or blue fluorescent protein in a mammal, one of ordinary skill in the art would not turn to Lin's teaching of detection of GFP in a transparent zebrafish as a solution. For the above reasons, the teachings of Lin are not germane to the teachings of Contag and Okabe.

As with claim 37, Contag and Okabe teach away from the subject matter of amended claim 39 and do not provide a reasonable expectation of success for the subject matter of amended claim

39. This is because claim 39, as with claim 37, requires expression of green of blue fluorescent protein in an internal organ. In view of these reasons and the irrelevance of Lin, Applicants respectfully submit that amended claim 39 is not obvious over Lin, Contag, and Okabe.

Conclusion

In view of the foregoing – the failure of the cited documents to teach two critical elements of the invention or to suggest them, applicants believe that claims 37 and 39 are in a position for allowance and passage of these claims to issue is respectfully requested.

Should minor issues remain that could be resolved over the phone, a telephone call to the undersigned would be appreciated.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing Attorney Docket No. 312762002710.

Respectfully submitted,

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